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Commentary

Six years after the NRC review of EPA's Draft IRIS Toxicological Review of Formaldehyde: Regulatory implications of new science in evaluating formaldehyde leukemogenicity

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ABSTRACT

Shortly after the International Agency for Research on Cancer (IARC) determined that formaldehyde causes leukemia, the United States Environmental Protection Agency (EPA) released its Draft IRIS Toxicological Review of Formaldehyde ("Draft IRIS Assessment"), also concluding that formaldehyde causes leukemia. Peer review of the Draft IRIS Assessment by a National Academy of Science committee noted that "causal determinations are not supported by the narrative provided in the draft" (NRC 2011). They offered recommendations for improving the Draft IRIS assessment and identified several important research gaps. Over the six years since the NRC peer review, significant new science has been published. We identify and summarize key recommendations made by NRC and map them to this new science, including extended analysis of epidemiological studies, updates of earlier occupational cohort studies, toxicological experiments using a sensitive mouse strain, mechanistic studies examining the role of exogenous versus endogenous formaldehyde in bone marrow, and several critical reviews. With few exceptions, new findings are consistently negative, and integration of all available evidence challenges the earlier conclusions that formaldehyde causes leukemia. Given formaldehyde's commercial importance, environmental ubiquity and endogenous production, accurate hazard classification and risk evaluation of whether exposure to formaldehyde from occupational, residential and consumer products causes leukemia are critical.

1. Introduction

Classification and regulation of human carcinogens is a key component to the protection and improvement of public health. However, proper regulation of industrial chemicals hinges on both valid hazard identification and quantitative risk assessment. Increasingly, hazard identification – at least where adequate scientific evidence is available – draws on critically assessing and integrating evidence across lines of inquiry including animal and human toxicology (e.g., pharmacokinetic, mechanistic studies) and epidemiology. Quantitative risk assessment requires reasonably accurate characterization of exposure, which is complicated, especially where historical measures are sparse or do not exist. Where adequate evidence from some or all of these is lacking, and where important uncertainties remain, policy-driven approaches favoring precaution are warranted. On the other hand, as evidence accumulates, more science-focused methods can be employed, reducing uncertainties, leading to sounder conclusions. Nevertheless, confident conclusions are sometimes drawn prematurely, as discussed in this commentary. Recent evaluations of formaldehyde, coupled with improved critical review and evidence integration expectations and new, more focused scientific evaluations, illustrate the dynamic nature of scientific inquiry, the need for parallel refinement of hazard characterization, and subsequently, stronger risk assessment.

In this paper, we illustrate the evolution of new scientific evidence on formaldehyde as a potential human leukemogen. The impetus for the new science summarized below is derived from the International Agency for Research on Cancer's (IARC) 2009 classification of formaldehyde as a known cause of leukemia in Monograph 100F (Baan et al., 2009; IARC, 2012), the US Environmental Protection Agency's (EPA's) similar classification in the Draft IRIS (Integrated Risk Information System) Toxicological Review of Formaldehyde – Inhalation Assessment (hereafter referred to as "Draft IRIS Assessment") (EPA, 2010), and the criticisms and recommendations presented in two National Academy of Science (NAS), National Research Council (NRC) expert reviews – one on the Draft IRIS Assessment and one on the IRIS process itself (NRC, 2011; NRC, 2014a). Various organizations and agencies have contributed to or sponsored the new science, including governments and universities, as well as industry. In revising and finalizing the Draft IRIS

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Table 1
Summary of major formaldehyde carcinogenicity classifications and noted scientific basis.

Year	Agency	Carcinogenicity Classification	Findings
1981	NTP (1981)	Anticipated to be a human carcinogen	Epidemiological evidence. Not discussed Toxicological evidence. One study cited (Swenberg et al., 1980). Nasal cancers: "While a full evaluation of the carcinogenicity of formaldehyde vapor must await completion of studies at the Chemical Industry Institute of Toxicology, evidence presented to date demonstrates that inhalation of formaldehyde results in a high incidence of nasal cancers in rats (Swenberg et al., 1980)."
1981 [a]	IARC (1982a; b)	Possibly carcinogenic to humans (Group 2B)	Epidemiological evidence. Inadequate (6 epidemiology studies) Toxicological evidence. Sufficient, formaldehyde is carcinogenic to rat, causes nasal cancers.
1982	NTP (1982)	Anticipated to be a human carcinogen	Epidemiological evidence. Inadequate (cites IARC, 1982a; b) Toxicological evidence. Sufficient, formaldehyde is carcinogenic to two strains of rats. Nasal cancers. One test in mice did not produce statistically significant results. Other studies in animals (mice and hamsters by inhalation exposure) were considered inadequate for evaluation.
1987 [b]	IARC (1987)	Probably carcinogenic to humans (Group 2A)	Epidemiological evidence. Limited Nasal cancers: Reported epidemiological evidence is strongest for nasal and nasopharyngeal cancer, noted limitations with small numbers of exposed cases and inconsistent reports. Leukemia: "Excess mortality from leukemia and cancer of the brain was generally not seen among industrial workers, which suggests that the excess for these cancers among professionals is due to conditions other than formaldehyde. The slight excesses of cancer among professionals noted in several studies generally did not display the patterns of increasing risk with various measures of exposure (i.e., latency, duration, level, or cumulative) usually seen for occupational carcinogens. No other cancer showed a consistent excess across the various studies." Toxicological evidence. Sufficient No changes in information reported from IARC (1982b) Supporting data. "In single studies of persons exposed to formaldehyde, increases in the frequencies of chromosomal aberrations and sister chromatid exchanges in peripheral lymphocytes have been reported, but negative results have also been published. The interpretation of both the positive and negative studies is difficult due to the small number of subjects studied and inconsistencies in the findings (IARC, Suppl 6, 1987)."
1991	EPA (1991)	Probable human carcinogen (Group B1)	Epidemiological evidence. Limited (28 studies considered) Nasal cancers: "Human data include nine studies that show statistically significant associations between site-specific respiratory neoplasms and exposure to formaldehyde or formaldehyde-containing products." (p.7) Leukemia: "Analysis of the remaining 19 studies indicate that leukemia and neoplasms of the brain and colon may be associated with formaldehyde exposure. The biological support for such postulates, however, has not yet been demonstrated." (p. 8) Toxicological evidence. Sufficient, nasal squamous cell carcinomas Increased incidence of nasal squamous cell carcinomas observed in rats and mice in long-term inhalation studies. Supporting data. "The classification is supported by in vitro genotoxicity data and formaldehyde's structural relationships to other carcinogenic aldehydes such as acetaldehyde." (p. 7)
1994 [c]	IARC (1995)	Probably carcinogenic to humans (Group 2A)	Epidemiological evidence. Limited Nasal cancers: Lack of consistency between cohort and case-control studies of cancers of the nasal cavities and paranasal sinuses. Leukemia: "The studies of industrial cohorts also showed low or no risk for lymphatic or hematopoietic cancers; however, the cohort studies of embalmers, anatomists and other professionals who use formaldehyde tended to show excess risks for cancers of the brain, although they were based on small numbers. These findings are countered by a consistent lack of excess risk for brain cancer in the studies of industrial cohorts, which generally included more direct and quantitative estimates of exposure to formaldehyde than did the cohort studies of embalmers and anatomists." (p. 334) Toxicological evidence. Sufficient (nasal squamous cell carcinomas) Squamous cell carcinomas of nasal cavities, at highest exposure. No evidence of carcinogenicity in hamsters. Mice showed no effect or were inadequate for evaluation. Supporting data. Genotoxic in variety of experimental systems in vivo. Induced DNA-protein cross-links, DNA single-strand breaks, chromosomal aberrations, sister chromatid exchange, gene mutation in human and rodent cells in vitro.

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Table 1 (continued)

Year	Agency	Carcinogenicity Classification	Findings
2004 [d]	IARC (2006)	Carcinogenic to humans (Group 1)	Epidemiological evidence. Sufficient, based on nasopharyngeal cancer Leukemia: "There is strong but not sufficient evidence for a causal association between leukemia and occupational exposure to formaldehyde. Increased risk for leukemia has consistently been observed in studies of professional workers and in two of three of the most relevant studies of industrial workers. These findings fall slightly short of being fully persuasive because of some limitations in the findings from the cohorts of industrial and garment workers in the USA and because they conflict with the non-positive findings from the British cohort of industrial workers." (p.276) Toxicological evidence. Sufficient (nasal squamous cell carcinoma) Supporting data. Mechanism for inducing myeloid leukema is not known. Possible mechanisms considered included clastogenic damage to circulatory stem cells. "The Working Group was not aware of any good rodent models that simulate the occurrence of acute myeloid leukemia in humans. Therefore, on the basis of the data available at this time, it was not possible to identify a mechanism for the induction of myeloid leukemia in humans." (p. 280)
2009 [e]	IARC (2012)	Carcinogenic to humans (Group 1)	Epidemiological evidence. Formaldehyde causes cancer of the nasopharynx and leukemia. "The Working Group was not in full agreement on the evaluation of formaldehyde causing leukemia in humans, with a small majority viewing the evidence as sufficient of carcinogenicity and the minority viewing the evidence as limited." (p. 430) Toxicological evidence. "Studies of bone marrow cells in formaldehyde-exposed animals have been inconsistent." (p.427) "Pancytopenia has not been among the haematological findings in experiments with laboratory animals exposed to relatively high doses of formaldehyde, including classic long-term safety assessment studies." (p.428) Inconsistent genotoxic effects in blood lymphocytes from animals exposed to formaldehyde via inhalation. Supporting data. "Particularly relevant to the discussions regarding sufficient evidence was a recent study accepted for publication which, for the first time, reported aneuploidy in blood of exposed workers characteristic of myeloid leukeaemia and myelodysplastic syndromes, with supporting information suggesting a decreased in the major circulating blood-cell types and in circulating haematological prescursor cells. The authors and Working Group felt that this study needed to be replicated." (p. 430) "Three possible mechanisms, all focused around genotoxicity, are moderately supported as the underlying mechanism for induction of haematological malignancies in humans. Further research is needed to decide which of the mechanisms is the most important." (p. 430)
2010	Draft IRIS Assessment (EPA, 2010)	Carcinogenic to humans	Epidemiological evidence. Sufficient. "Human epidemiological evidence is sufficient to conclude a causal association between formaldehyde exposure and nasopharyngeal cancer, nasal and paranasal cancer, all leukemias, ML and lymphohematopoietic cancers as a group" (p. 6–46). All LHM combined: "Given the consistency and strength of the positive associations for all LHP [lymphohematopoietic] cancer mortality in professional cohorts (embalmers, anatomists and pathologists) taken together with the strong positive results of the NCI cohort, human epidemiologic evidence are [sic] sufficient to conclude that there is a causal association between formaldehyde exposure and mortality from all LHP malignancies (as a group.)" (p. 4–180). All leukemias as a group: "While the epidemiologic evidence for a causal association between formaldehyde and all leukemia as a group is not at [sic] strong as for all LHP as a group, the repeated identification of an association in multiple meta-analyses taken together with the clear causal association between myeloid leukemia demonstrated by Hauptmann et al. (2009) and the consistent evidence reported by Beane Freeman et al. (2009) are sufficient to conclude that there is a causal association between formaldehyde exposure and mortality from all leukemia as a group." (p. 4–182) Myeloid leukemia: "Given the consistency of the positive associations for formaldehyde with myeloid leukemia cancer mortality across five of the six studies (Hauptmann et al., 2009; Pinkerton et al., 2003; Hayes et al., 1990; Stroup et al., 1986; Walrath and Fraumeni, 1984, 1983; but not Beane Freeman et al., 2009), the statistically significant meta-analysis by Zhang et al. (2009) and the convincing results from Hauptmann et al. (2009), the human epidemiologic evidence is sufficient to conclude that there is a causal association between formaldehyde exposure and mortality from myeloid leukemia." (p. 4–185) Toxicological evidence. Limited evidence to support conclusion that formaldehyde exposure causes leukemia. Four studies evaluated the leukemic potential of formaldehyde. "Inhalation exposure of formaldehyde increased lymphoma in female mice and leukemia in female F344 rats, but not male rats (Battelle Columbus Laboratories, 1981). No increases in leukemia or lymphoma were seen in male Wistar rats when exposed to formaldehyde in drinking water (Til et al., 1989) or male rats after chronic inhalation exposures (Sellakumar et al., 1985)." (p. 6–21) Supporting data. "Chromosomal damage in blood-borne immune cells, relevant to agent-induced lymphohematopoietic cancers has been coumented in formaldehyde exposed workers, including increased micronuclei and chromosomal aberrations, increased incidence and aneuploidy in hematopoietic stem cells." (p. 6–22)

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Table 1 (continued)

Year	Agency	Carcinogenicity Classification	Findings
2012	NTP (2011)	Known to be a human carcinogen	Epidemiological evidence. Causes nasopharyngeal cancer, sinonasal cancer, and myeloid leukemia "Epidemiological studies have demonstrated a causal relationship between exposure to formaldehyde and cancer in humans. Causality is indicated by consistent findings of increased risks of nasopharyngeal cancer, sinonasal cancer, and lymphohematopoietic cancer, specifically myeloid leukemia among individuals with higher measures of exposure to formaldehyde (exposure level or duration), which cannot be explained by chance, bias, or confounding. The evidence for nasopharyngeal cancer is somewhat stronger than that for myeloid leukemia." (p. 195) Toxicological evidence. No specific evidence cited regarding leukemia beyond the following: "Hemolymphoreticular tumor (combined types) in rats of both sexes also were significantly increased after long-term exposure of adults; however, it is unclear whether these turmos were exposure-related, because of limitations in the reporting of these tumors (Soffritti et al., 2002)." (p. 198) Supporting data. "Lymphohematopoietic cancers are a heterogeneous group of cancers that arise from damage to stem cells during hematopoietic and lymphoid development (Greaves, 2004). Blood cells arise from a common stem cell, which forms two progenitor cells, the common myeloid stem cell and the common lymphoid stem cell. Most agents known to cause leukemia are thought to do so by directly damaging stem cells in the bone marrow. In order for a stem cell to become malignant, it must acquire genetic mutations and genomic instability (Zhang et al., 2010a). Because formaldehyde is highly reactive and rapidly metabolized, a key question is how it can reach the bone marrow or cause toxicity or genotoxicity at distal sites. The endogenous concentration in the blood of humans, monkeys, and rats is about 2–3 μg/g, and the concentration does not increase after inhalation of formaldehyde from exogenous sources (Heck et al., 1985; Casanova et al., 1988; Heck and Casanova, 2004). Moreover, N2-hydroxymethyl-dG–DNA adducts have not been detected at distal sites in rats (such as the bone marrow, white blood cells, lung, spleen, liver, or thymus) (Lu et al., 2010). For these reasons, the plausibility of formaldehyde's causing cancer at distal sites, such as myeloid leukemia, has been questioned (Golden et al., 2006; Pyatt et al., 2008). However, systemic effects have been observed after inhalation or oral exposure, and although the mechanisms by which formaldehyde causes myeloid leukemia in humans are not known, a number of plausible mechanisms have been advanced. These include (1) theoretical mechanisms for the distribution of formaldehyde to distal sites and (2) proposed mechanisms of leukemogenesis that do not require formaldehyde to reach the bone marrow. In addition, there is some evidence that formaldehyde causes adverse haematological effects in humans." (p. 199)
2012	RAC (2012)	Carc. 1B - H50 [f] May cause cancer	Epidemiological evidence. Limited "In conclusion, while some studies have found increased rates of leukemia, the epidemiology data do not show consistent findings across studies for leukemia rates. The inconsistent findings across job types and exposure groupings, and the lack of biological plausibility argue against formaldehyde as the cause of the increased rates. The findings of slightly increased leukemia rates among embalmers, pathologist and anatomists, but not among industrial workers, suggests the possibility of confounding factors that bear investigation. Results based on cohort and case-control studies do not suggest an association between formaldehyde exposure and leukemia." (p.41) Toxicological evidence. "No indication of carcinogenic potential on organs/tissues distant from the site of contact (respiratory tract) including lymphohaematopoietic tumors in inhalation study of rats and mice (Kerns et al., 1983)." (p.22) Supporting data. "Physiologically, formaldehyde occurs in most organisms, tissues and cells at very low concentrations. In mammals, formaldehyde is found at values of about 0.1 mM in blood (man, monkey, rat). The physiological blood formaldehyde levels in humans, rats and monkeys were not elevated after parenteral exposure, indicating a very low systemic tissue and organ distribution of formaldehyde. These findings support evidence that formaldehyde shows local reactivity and elicits its toxic potential focally and predominantly at deposition areas such as epithelia of the upper respiratory tract, the oro-gastric tract as well as the skin. (BfR-Wissenschaft, 2006). Thus, it may be expected that carcinogenic effects are not found at anatomical sites distant from the port of entry." (p.44)

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Table 1 (continued)

Year	Agency	Carcinogenicity Classification	Findings
2016	Scientific Committee on Occupational Exposure Limits for Formaldehyde (Bolt et al., 2016)	Carcinogen Group C (genotoxic carcinogen with a mode-of-action based threshold)	Epidemiological evidence. Limited. Leukemias: "A possible induction of myeloid leukaemias by FA in humans is not so easy to explain, but there are indications that FA might induce this kind of malignancy. However, this would require that FA would act systemically and reach the bone marrow, which is the target tissue. Such an action would not be possible within a range where the external dose does not change the physiological level of FA." (p.45) Toxicological Evidence. "In essence, new experimental data, reported since 2008, clearly indicate that systemic genotoxic action of inhaled FA is not likely, even at exposure concentrations leading to nasal malignancies in the rat." (p.49) Supporting Data. "A plethora of arguments suggests that FA concentrations below 1 or 2 ppm would not increase the risk of cancer in the nose or any other tissue, or affect FA homeostasis within epithelial cells (Swenberg et al., 2013)." (p. 49)

[a] IARC Working Group met February 1981. IARC Preamble (1982): "For many of the chemicals evaluated in the first 29 vol of the/ARC Monographs for which there is sufficient evidence of carcinogenicity in animals, data relating to carcinogenicity for humans are either insufficient or nonexistent. In the absence of adequate data on humans, it is reasonable, for practical purposes, to regard chemicals for which there is sufficient evidence of carcinogenicity in animals as if they presented a carcinogenic risk to humans. The use of the expressions 'for practical purposes' and 'as if they presented a carcinogenic risk' indicates that at the present time a correlation between carcinogenicity in animals and possible human risk cannot be made on a purely scientific basis, but only pragmatically. Such a pragmatical correlation may be useful to regulatory agencies in making decisions related to the primary prevention of cancer."

[b] IARC Working Group met March 1987.

[c] IARC Working Group met October 1994; monograph published 1995.

[d] IARC Working Group met June 2004; monograph published 2006.

[e] IARC Working Group met October 2009; monograph published 2012.

[f] EU harmonized classification and labelling.

Assessment (EPA, 2010), EPA now has the opportunity to incorporate the new evidence in addressing many of the issues raised by the NRC reviews.

2. Formaldehyde cancer hazard evaluation

The carcinogenicity of formaldehyde has been evaluated by several agencies since the early 1980s, including the IARC, the National Toxicology Program (NTP) of the National Institute for Environmental Health Sciences (NIEHS), the EPA, and most recently, the Committee for Risk Assessment (RAC) of the European Chemicals Agency (ECHA), and the Scientific Committee on Occupational Exposure Limits (SCOEL) of the European Commission (Table 1). Except for the RAC review (RAC, 2012) and the SCOEL review (Bolt et al., 2016), which re-classified formaldehyde as a Carcinogen Category 1B (i.e., presumed to have carcinogenic potential for humans) and a Category C carcinogen (i.e., genotoxic carcinogen with a mode of action based threshold), respectively, these reviews classified formaldehyde as a known human carcinogen, primarily based on NPC but also on lymphohematopoietic malignancies (LHM) as a group and/or all leukemias as a group, and all myeloid leukemias (ML) as a group (EPA, 2010; IARC, 2012; NTP, 2011). Differences between NTP (2011) and EPA draft classifications (final version of the EPA review is pending) have been highlighted by Rhomberg (2015a) and differences between the IARC (2012) and the RAC (RAC, 2012) evaluations have been discussed by Marsh et al. (2014).

The reviews by authoritative bodies acknowledged that hazard identification for formaldehyde was not straightforward, especially with respect to possible leukemogenicity, in part due to its endogenous production and high reactivity. This prompted closer scrutiny regarding the methods used to critically evaluate the strength and quality of scientific studies, and ultimately, how best to integrate evidence across lines of inquiry such as animal, mechanistic and epidemiological evaluations.

IARC first classified formaldehyde as "carcinogenic to humans" (i.e., Group 1) in 2005 (Cogliano et al., 2005; IARC, 2006), revising the previous evaluation in 1995 that formaldehyde is "probably carcinogenic to humans" (i.e., Group 2A) (Table 1). The 2005 evaluation (Cogliano et al., 2005; IARC, 2006) concluded that formaldehyde causes NPC, based primarily on results from animal studies, with additional evidence from "the largest and most informative cohort study of industrial workers" (i.e., Hauptmann, et al., 2004). Results from animal studies demonstrated that formaldehyde in direct contact with nasal passage tissues induced tumors at formaldehyde concentrations > 2 parts per million (ppm) as summarized by Nielsen et al. (2013) and later by Nielsen et al. (2017). This was considered consistent with formaldehyde's demonstrated genotoxicity, and with the "sufficient epidemiological evidence that formaldehyde causes nasopharyngeal cancer in humans" (IARC, 2006).

IARC (2012) concluded that formaldehyde also causes leukemia, and in particular ML, although the Working Group noted that it was a "small majority" who found the evidence to be sufficient. Neither Hauptmann et al. (2003) nor the subsequently updated study (Beane Freeman et al., 2009) published results specifically for acute myeloid leukemia (AML). The Working Group noted a study reporting aneuploidy in the blood of exposed workers (Zhang et al., 2010a), recently accepted for publication, provided supporting data, with the caveat that the study needed to be replicated (IARC, 2012). Indeed, proper replication of this study is still needed, because the study protocol was not consistent with adequate cell counting standards, including the authors' earlier descriptions of the OctoChrome FISH method (Zhang et al., 2005; Zhang et al., 2011) and other standards (American Society of Medical Genetics, 2006). One particular challenge is that occupational exposure limits in North America, Europe and in many countries around the world protect workers from the levels of occupational formaldehyde exposures that were studied by Zhang et al. (2010a) in China making replication of the study logistically difficult. Proper replication of this study also will require use of methods to successfully distinguish between aneuploidy arising in vivo from aneuploidy that arises during the period of in vitro culture, as discussed in section 3.3.3 below.

Following the IARC review and classification, the National Toxicology Program (NTP) concluded in the 12th Report on Carcinogens (12th RoC) that formaldehyde causes nasopharyngeal cancer and myeloid leukemia (NTP, 2011) (Table 1). The 12th RoC stated "The most informative studies for evaluation of the risk of ML are the large cohort studies of industrial workers (the NCI, NIOSH, and

British cohorts) and the NCI nested case-control study[1] of lymphohematopoietic cancer in embalmers" and specifically that "Three of these four studies found elevated risks of myeloid leukemia among individuals with high exposure to formaldehyde, as well as positive exposure-response relationships". However, the NTP also noted "In the large cohort of British chemical workers, no increased risk of leukemia was found for formaldehyde exposure" and that in the only case-control study examining ML (Blair et al., 2000) "an excess risk was found for chronic (but not acute) myeloid leukemia" (NTP, RoC, 12th edition, "Formaldehyde", p.3).

2.1. Environmental Protection Agency integrated risk assessment program (IRIS)

Formaldehyde had been classified by the EPA as a "probable" human carcinogen (Group B1) in 1991 (Table 1). An updated assessment for public review and comment was first released in June 2010, 12 years after the EPA announced the re-evaluation, and the draft assessment reported that formaldehyde causes NPC, nasal and paranasal cancer, lymphohematopoietic cancers, all leukemias, and ML (Table 1). The EPA (2010) also derived a draft inhalation unit risk (IUR) value of 8.1×10^{-2} per ppm (6.6×10^{-5} per $\mu g/m^3$)[2] based on the upper bound on the sum of the risk estimates for NPC, Hodgkin lymphoma, and leukemia (combined risks) based on part of the results reported in Beane Freeman et al. (2009). For rationale, the EPA said the classification "is supported by cohort analyses of embalmers, pathologists and anatomists (Hall et al., 1991; Hayes et al., 1990; Levine et al., 1984; Matanoski, 1989; Stroup et al., 1986; Walrath and Fraumeni, 1983, 1984)" despite the observation that "... SMR analyses of the large industrial cohorts do not indicate a similar association (Beane Freeman et al., 2009; Coggon et al., 2003; Pinkerton et al., 2004)" (EPA, 2010; page 4–180). The EPA also cited three meta-analyses (Bosetti et al., 2008; Collins and Lineker, 2004; Zhang et al., 2009) that largely included the same studies as providing additional evidence. Repeatedly reporting the same results, however, does not constitute independent or additional evidence. Similarly, all meta-analyses included earlier versions of the NCI cohort workers and embalmers studies and therefore, the meta-analyses, too, are redundant with the updated analyses of the NCI cohort workers and embalmers studies.

The conclusions in the Draft IRIS Assessment specific to myeloid leukemia are as follows:

> "Given the consistency of the positive associations for formaldehyde with myeloid leukemia cancer mortality across five of the six studies (Hauptmann et al., 2009; Hayes et al., 1990; Pinkerton et al., 2004; Stroup et al., 1986; Walrath and Fraumeni 1983, 1984; but not Beane Freeman et al., 2009), the statistically significant meta-analysis by Zhang et al. (2009) and the convincing results from Hauptmann et al. (2009), the human epidemiologic evidence is sufficient to conclude that there is a causal association between formaldehyde exposure and mortality from myeloid leukemia." (EPA, 2010; pages 4–184, 4–185)

Again, because of the significant overlap between Hauptmann et al. (2009) and the three PMR studies of funeral directors and embalmers (Hayes et al., 1990; Walrath and Fraumeni, 1983; 1984) these reports do not constitute independent evidence or consistency across studies. Hauptmann et al. (2009) has been judged to have severe methodological flaws (Cole et al., 2010a; b). Separately, the Zhang et al. (2009) meta-analysis combined different exposure metrics (peak, average intensity, cumulative exposure, duration), and thus, the exposure metrics were not comparable across studies. A more methodologically rigorous approach would be to perform meta-analyses for similar exposure metrics, that is, a meta-RR for cumulative exposure, meta-RR for average exposure, meta-RR for duration of exposure (only one study reported results in relation to peak exposure, precluding a meta-analysis for peak exposure). As such, the Zhang et al. (2009) meta-analysis results are difficult to interpret and methodologically flawed. Finally, combining data in a meta-analyses does not overcome any systematic biases in the underlying studies (Greenland and Longnecker, 1992).

2.2. National academies peer-review process

The NRC of the NAS, at the request of the EPA, formed an expert Committee to perform the peer-review of the Draft IRIS Assessment. Following a series of meetings during the second half of 2010, the NRC issued the final peer-review report on April 8, 2011 (NRC, 2011) as a pre-publication copy. The Committee identified numerous constructive criticisms and data gaps, and provided recommendations for improving IRIS reviews in general (NRC, 2011). Though not directly charged to evaluate the Draft IRIS Assessment conclusions, the peer review raised important questions regarding the underlying methods giving rise to several conclusions, including the basic causal conclusions:

> "EPA evaluated the evidence of a causal relationship between formaldehyde exposure and several groupings of LHP cancers—"all LHP cancers," "all leukemias," and "myeloid leukemias." The committee does not support the grouping of "all LHP cancers" because it combines many diverse cancers that are not closely related in etiology and cells of origin. The committee recommends that EPA focus on the most specific diagnoses available in the epidemiologic data, such as acute myeloblastic leukemia, chronic lymphocytic leukemia, and specific lymphomas." (NRC, 2011; page 11)

The Committee concluded that EPA's claims that formaldehyde causes leukemia, ML or related hematopoietic cancers were not supported in EPA's assessment, appeared to be subjective in nature, and that no clear scientific framework had been applied by EPA in reaching that conclusion (NRC, 2011). The absence of such a framework was judged by the committee as problematic:

> "As with the respiratory tract cancers, the draft IRIS assessment does not provide a clear framework for causal determinations. As a result, the conclusions appear to be based on a subjective view of the overall data, and the absence of a causal framework for these cancers is particularly problematic given the inconsistencies in the epidemiologic data, the weak animal data, and the lack of mechanistic data. Although EPA provided an exhaustive description of the studies and speculated extensively on possible modes of action, the causal determinations are not supported by the narrative provided in the draft IRIS assessment. Accordingly, the committee recommends that EPA revisit arguments that support determinations of causality for specific LHP cancers and in so doing include detailed descriptions of the criteria that were used to weigh evidence and assess causality. That will add needed transparency and validity to its conclusions." (NRC, 2011; page 11)

The NRC peer review further pointed out that the EPA (2010) conclusion that formaldehyde causes ML was based primarily on selected epidemiological studies, and other streams of evidence (animal, mode of action) were not considered beyond studies conducted by Zhang et al. (2009, 2010a).

In the 7th and final chapter of its review, entitled, "A Roadmap for Revision," the NRC provided recommendations in two categories: "Critical Revisions of the Current Draft IRIS Assessment of

[1] This study technically is not a "nested case-control study" but rather a pooled reanalysis of death certificate data from several published proportionate mortality ratio (PMR) analyses, using a case-control approach. Thus, it carries the same limitations of death certificate analyses performed outside of a well enumerated cohort, and therefore is not "nested" in any true cohort that could be accurately enumerated.

[2] This is 15 times higher than the inhalation unit risk (IUR) derived by EPA for vinyl chloride (4.4×10^{-6} per $\mu g/m^3$) (EPA, 2000; page 50), a chemical for which the evidence clearly supports a causal association between exposure and effects in both animals and humans.

Formaldehyde," and "Future Assessments and the IRIS Process" (NRC, 2011). NRC (2011) specifically identified the systematic review standards adopted by the Institute of Medicine (IOM), as being appropriate for such an analysis (IOM, 2011).

Following the release of the NRC (2011) peer review, Congress issued House Report No. 112–151 (US U.S. House, 2011), and directed EPA to incorporate recommendations of Chapter 7 of the NRC (2011) peer-review report into the IRIS process. In 2014, NRC released an additional report on the IRIS process (NRC, 2014a), and emphasized the importance of evidence integration for hazard identification, in which studies of higher quality and low risk of bias are given greater weight in drawing conclusions regarding causality.

As part of their response to the NRC reviews, the EPA convened a state-of-the-science workshop on formaldehyde on April 30 and May 1, 2014 in Arlington, Virginia. This workshop focused on three themes:

> Evidence pertaining to the influence of formaldehyde that is produced endogenously (by the body during normal biological processes) on the toxicity of inhaled formaldehyde, and implications for the health assessment;
> Mechanistic evidence relevant to formaldehyde inhalation exposure and lymphohematopoietic cancers (leukemia and lymphomas); and Epidemiological research examining the potential association between formaldehyde exposure and lymphohematopoietic cancers (leukemia and lymphomas).
> (From: https://www.epa.gov/iris/formaldehyde-workshop)

A second workshop was announced at the meeting but never convened. Since then, the EPA submitted a progress report to Congress in 2015 (EPA, 2015) in response to a request from Congress (U.S. House, 2014, p. 59). Most recently, House Report No. 114–632 (U.S. House, 2016; page 57–59) and Senate Report No. 114–281 (U.S Senate, 2016; page 62) have requested the allocation of funds for NRC to peer review the revised IRIS Toxicological Review of Formaldehyde, to ensure that recommendations raised by the NRC (2011) were implemented.

3. New studies published since the 2011 NRC peer review of the draft IRIS assessment

Numerous studies and updated analyses have been published since the 2011 NRC peer review of the Draft IRIS Assessment, the findings of which, at least in part, fill many of the "data gaps" and address several key methodological issues highlighted in the NRC Committee recommendations (NRC, 2011). Below we summarize this new research, organized around the data streams (e.g., epidemiological, toxicological, and mode of action) for evidence integration and quantification of potential leukemia risks, specifically responsive to the following NRC recommendations (2011) (page reference provided):

Epidemiological Evidence

> Discussion of the specific strengths, weaknesses and inconsistencies in several key studies, as the draft IRIS assessment relies solely on epidemiologic studies to determine causality. (p.113)
> Clarification of the basis of the EPA's interpretations of the Beane Freeman et al. (2009) results regarding the various dose metrics (peak versus cumulative) and the various LHP cancers. (p.113)
> Evaluation of the most specific diagnoses available in the epidemiologic data (i.e., acute myeloblastic leukemia, chronic lymphocytic leukemia, and other specific lymphomas). (p. 113)

Toxicological Evidence

> Paucity of evidence of formaldehyde-induced LHP cancers in animal models. EPA's unpublished re-analysis of the Battelle chronic experiments in mice and rats (Battelle Columbus Laboratories, 1981), although intriguing, provides the only positive findings and thus does not contribute to the weight of evidence of causality. (p.110)

Mode of Action Evidence

> Improving the understanding of when exogenous formaldehyde exposure appreciably alters normal endogenous formaldehyde concentrations. (p. 58)
> Reconciliation of divergent statements regarding systemic delivery of formaldehyde, (p.59) as direct evidence of systemic delivery of formaldehyde is generally lacking. (p.5)
> Data are insufficient to conclude definitively that formaldehyde is causing cytogenetic effects at distant sites. (p. 5)

Dose-Response Assessment

> Independent analyses of the dose-response models to confirm the degree to which the models fit the data appropriately. (p. 14)
> Consideration of the use of alternative extrapolation models for the analysis of the cancer data. (p.14)
> Further justification of the selection and use of the NCI cohort (Beane Freeman et al., 2009) for calculation of unit risk because the cumulative exposure metric (used in the calculation of unit risk) was not related to leukemia risk in the NCI cohort. (p.112)

Methods for Evidence Integration

> Development of an approach to weight of evidence that includes "a single integrative step after assessing all of the individual lines of evidence". Although a synthesis and summary are provided, the process that EPA used to weigh different lines of evidence and how that evidence was integrated into a final conclusion are not apparent in the draft assessment and should be made clear in the final version. (p. 113)

A summary of each of these recommendations and data gaps, along with the new science that has been conducted to address them is provided in Table 2 and discussed in the following sections.

3.1. Epidemiological evidence

The NRC peer review called attention to the EPA's sole reliance on epidemiological studies to determine causality, rather than integrating epidemiology data with the toxicological and mechanistic evidence. When inferring causation from epidemiology studies, the evidence is critically assessed and synthesized across a body of individual studies, with greater weight assigned to studies of higher quality (rather than assigning equal weight to each). Better epidemiological studies are those that implement individual level exposure data, and minimize the potential for systematic bias and confounding. The ascertainment of outcome and analysis using accurate (and specific) diagnosis are also critical in the causal evaluation. The NRC peer review noted that the grouping of "all LHPs" comprises 14 biologically distinct diagnoses in humans and should not be used in determinations of causality. There is some evidence that these diseases may originate from the same stem cell line (Gluzman et al., 2015; Goldstein, 2010) and could therefore arise from direct effects on these cells. There are no studies, however, that demonstrate an effect on these stem cells following exposure to formaldehyde. The largest population of these stem cells would be found in the bone marrow, and, based on the available evidence, inhaled formaldehyde appears incapable of reaching the bone marrow (see Section 3.3.2). The affected cells would need to be circulating stem cells that encounter formaldehyde at the portal of entry (i.e., the nose or upper airways) and then return to the bone marrow.

After the NRC peer review was published, Checkoway et al. (2012) critically reviewed the epidemiological evidence and reported inconsistent and sporadic associations between formaldehyde exposure and various specific LHM, including ML. Only a few epidemiology studies considered AML specifically. Since the critical review (Checkoway et al., 2012), several additional epidemiological studies have been published that provide insights on formaldehyde exposure and AML risk and address other specific issues raised by the 2011 NRC peer review. The key strengths and limitations of these studies are highlighted below.

Table 2
Summary of NRC (2011) comments or identified data gaps and new formaldehyde science by lines of inquiry.

NRC (2011) Comment/Identified Data Gap	New Formaldehyde Science
A. Epidemiological Evidence	
Evaluation of the most specific diagnoses available in the epidemiologic data (i.e., acute myeloblastic leukemia, chronic lymphocytic leukemia, and other specific lymphomas). (NRC, p. 113)	New analyses of the NCI formaldehyde workers cohort specifically for AML are reported. Results do not support the hypothesis that formaldehyde causes AML. See: Checkoway et al., 2015 Associations seen between formaldehyde exposure and Hodgkin lymphoma and chronic myeloid leukemia (CML) have not been observed in other studies and are not considered plausible. See: Checkoway et al., 2015
Because the draft IRIS assessment relies solely on epidemiologic studies to determine causality, further discussion of the specific strengths, weaknesses, and inconsistencies in several key studies is needed. (NRC, p. 113)	A critical review of the epidemiological literature indicated no consistent or strong epidemiologic evidence that formaldehyde is causally related to any lymphohematopoetic malignancies. The absence of established toxicological mechanisms further weakens any arguments for causation. See: Checkoway et al., 2012
Clarification of the basis of its interpretations of the results regarding the various dose metrics (peak versus cumulative) and the various LHP cancers. (NRC, p. 112–113)	Acute myeloid leukemia (AML) was unrelated to cumulative, average or peak exposure, and few deaths occurred within 20 or more years of last peak exposure. Suggestive associations with peak exposure were observed for chronic myeloid leukemia, based on very small numbers. Hodgkin lymphoma relative risk estimates suggested trends for both cumulative (p_{trend} = 0.05) and peak (p_{trend} = 0.003) exposures. However, no other lymphohematopoietic malignancy was associated with either cumulative or peak exposure. See: Checkoway et al., 2015
The selection and use of the NCI cohort (Beane Freeman et al., 2009) should be further justified. (NRC, p. 112)	Extended follow-up of a cohort of 14,008 chemical workers at 6 factories in England and Wales, covering the period 1941–2012. Results provide no support for an increased hazard of myeloid leukemia from formaldehyde exposure. See: Coggon et al., 2014 Extended follow-up of 11,098 employees of three garment manufacturing facilities. Results demonstrated limited evidence for formaldehyde exposure and any LHM including AML, based on 14 observed cases. See: Meyers et al., 2013
B. Toxicological Evidence	
Paucity of evidence of formaldehyde-induced LHP cancers in animal models. EPA's unpublished re-analysis of the Battelle chronic experiments in mice and rats (Battelle Columbus Laboratories, 1981), although intriguing, provides the only positive findings and thus does not contribute to the weight of evidence of causality. (NRC, p. 110)	No cases of leukemia or lymphohematopoietic neoplasia were seen. FA inhalation did not cause leukemia in genetically predisposed C3B6·129F1-Trp53tm1Brd mice. See: Morgan et al., 2017 FA inhalation did not cause leukemia or lymphohematopoietic neoplasia in genetically predisposed p53-Haploinsufficient mice. See: Morgan et al., 2017
C. Mode of Action Evidence	
Improve understanding of when exogenous formaldehyde exposure appreciably alters normal endogenous formaldehyde concentrations. (NRC, p. 58)	Endogenous formaldehyde in nasal tissues did not significantly affect flux or nasal uptake predictions at exposure concentrations > 500 ppb; however, reduced nasal uptake was predicted at lower exposure concentrations. See: Schroeter et al. (2014) With the application of highly sensitive instruments and accurate assays, inhaled formaldehyde was found to reach nasal respiratory epithelium, but not other tissues distant to the site of initial contact. In contrast, endogenous adducts were readily detected in all tissues examined with remarkably higher amounts present. Moreover, the amounts of exogenous formaldehyde-induced adducts were 3- to 8-fold and 5- to 11-fold lower than the average amounts of endogenous formaldehyde-induced adducts in rat and monkey nasal respiratory epithelium, respectively. See: Yu et al., 2015
Reconcile divergent statements regarding systemic delivery of formaldehyde (p.59); direct evidence of systemic delivery of formaldehyde is generally lacking. (NRC, p.5)	Based on a sensitive analytical method that can measure endogenous versus exogenous formaldehyde DNA adducts, the multiple studies demonstrated that inhaled exogenous formaldehyde only reached rat or monkey noses, but not tissues distant to the site of initial contact. Also, new evidence suggests that endogenous formaldehyde in bone marrow is toxic and carcinogenic, and may cause leukemia (but not exogenous formaldehyde). See: Lai et al., 2016; Pontel et al., 2015; Yu et al., 2015; Edrissi et al., 2013; Moeller et al., 2011; Lu et al., 2011
Data are insufficient to conclude definitively that formaldehyde is causing cytogenetic effects at distant sites. (NRC, p. 5)	Critical review of the genotoxicity literature found no convincing evidence that exogenous exposures to FA alone, and by inhalation, induce mutations at sites distant from the portal of entry tissue as a direct DNA reactive mutagenic effect – specifically, not in the bone marrow. Review of the existing studies of hematotoxicity, likewise, failed to demonstrate myelotoxicity in any species– a probable prerequisite for leukemogenesis. See: Albertini and Kaden, 2016 Reanalysis of selected raw data from the Zhang et al. (2010a) study do not support a causal association between formaldehyde and myeloid leukemia or lymphoid malignancies. Because of the significant methodological limitations, unless the results can be confirmed using appropriate methodologies designed to detect in vivo events, the reanalysis of the results provided by Zhang et al. (2010a) raise sufficient questions that limit the use of Zhang et al. (2010a) to support the hypothesis that formaldehyde exposure is causally related to leukemia or lymphoid malignancies. See: Gentry et al. (2013) Additional analyses were performed on the study data obtained from the original study (Zhang et al., 2010a) including individual average formaldehyde exposure concentration measurements performed for each exposed worker. The objective was to evaluate haematological parameters and aneuploidy in relation to quantitative exposure measures of formaldehyde. Results showed that differences in white blood cell, granulocyte, platelet, and red blood cell counts were not exposure-dependent. Furthermore, among formaldehyde-exposed workers, no association was observed between individual average formaldehyde exposure estimates and frequency of aneuploidy, suggested by the original study authors to be indicators of myeloid leukemia risk. See: Mundt et al., 2017
D. Dose-Response Assessment	
Independent analysis of the dose-response models is needed to confirm the degree to which the models fit the data appropriately. (NRC, p. 14)	The documentation of the methods applied in the Draft IRIS Assessment (EPA, 2010) lacks sufficient detail for duplication of the unit risk estimates provided, even with the availability of the raw data from the NCI cohort study (Beane Freeman et al., 2009). This

(continued on next page)

Table 2 (continued)

NRC (2011) Comment/Identified Data Gap	New Formaldehyde Science
	lack of transparency and detail may result in different estimates of unit risks, especially as initial analyses resulted in a lack of a significant dose-response relationship for selected endpoints. See: Van Landingham et al., 2016
BBDR models developed by Conolly and co-workers should be used. (p.58) These models are biologically motivated and mechanistic; requiring that all relevant data be reconciled with the model. (NRC, p.57)	Expansion of the model to incorporate recent data on endogenous levels of formaldehyde is in development. This will incorporate the most recent science to better understand when exogenous formaldehyde exposure appreciably alters normal endogenous formaldehyde concentrations. Work in progress: Clewell et al., unpublished
Consideration of the use of alternative extrapolation models for the analysis of the cancer data. (NASNRC, p.14)	Results of the "bottom-up " approach indicate that recent top-down risk extrapolations from occupational cohort mortality data for workers exposed to formaldehyde are overly conservative by substantial margins. See: Starr and Swenberg, 2013 Updated "bottom-up" risk estimates heighten the marked contrasts that are present between the previous estimates and the corresponding USEPA estimates, with the larger difference for leukemia being due primarily to the significantly improved detection limit for the analytical method used in quantitating DNA adduct numbers. See: Starr and Swenberg, 2016
E. Methods for Evidence Integration	
EPA's approach to weight of evidence should include "a single integrative step after assessing all of the individual lines of evidence." Although a synthesis and summary are provided, the process that EPA used to weigh different lines of evidence and how that evidence was integrated into a final conclusion are not apparent in the draft assessment and should be made clear in the final version. (NRC, p. 113)	A hypothesis-based weight-of-evidence (HBWoE) approach was conducted to evaluate the large body of evidence regarding formaldehyde and leukemogenesis, attending to how human, animal, and mode-of-action results inform one another. Upon comparison of alternative proposals regarding what causal processes may have led to the array of observations, it was concluded that the case for a causal association is weak and strains biological plausibility. Instead, apparent association between formaldehyde inhalation and leukemia in some human studies is better interpreted as due to chance or confounding. See: Rhomberg et al., 2011 Additional frameworks have been developed to integrate evidence. See: Adami et al., 2011; Lavelle et al., 2012; Linkov et al., 2015; Rhomberg 2015b; Rooney et al., 2014; Woodruff and Sutton, 2014. Other agencies or advisory bodies have conducted assessments of the carcinogenicity of formaldehyde in a transparent manner. See: RAC, 2012; Bolt et al., 2016; Nielsen et al., 2017

3.1.1. Key studies and their strengths and limitations

Since the update of mortality in the US formaldehyde users and producers cohort (Beane Freeman et al., 2009), two other large industrywide cohort mortality studies have been updated: the NIOSH garment workers (Meyers et al., 2013) and the UK industry-wide formaldehyde producers and users (Coggon et al., 2014). In addition, a large population registry-based case-control study of incident AML cases in the Nordic countries, a small occupational study in Italy and a large multicenter European study of occupational exposures in a cohort established to study nutritional and metabolic risk factors in cancer risks have been published (Pira et al., 2014; Saberi Hosnijeh et al. 2013; Talibov et al., 2014).

3.1.1.1. NIOSH cohort study of garment workers. Meyers et al. (2013) updated mortality from 1960 through 2008 for 11,043 US garment workers exposed to formaldehyde who worked for at least three months between 1955 and 1983 at three US factories. A total of 36 leukemia deaths was reported (SMR = 1.04, 95% CI 0.73–1.44, compared to US mortality rates), of which 21 were ML (14 AML, 5 chronic myeloid leukemia (CML), 2 other and unspecified ML). Although this study did not link quantitative estimates of formaldehyde exposure to study subjects, an industrial hygiene survey during the early 1980s reported that formaldehyde concentrations were similar across all departments and facilities, and the overall geometric mean was 0.15 ppm with a geometric standard deviation of 1.90 (Stayner et al., 1988). The formaldehyde resins used to treat permanent press fabrics had been reformulated over time, and as a result, the formaldehyde concentrations measured in the early 1980s were believed to be lower than the approximately 4 ppm estimated by NRC for years prior to 1970 (NRC, 2014b). Meyers et al. (2013) reported an SMR for AML of 1.22 (95% CI 0.67–2.05), noting that NIOSH investigators "continue to see limited evidence of an association between formaldehyde and leukemia" and that "the extended follow-up did not strengthen previously observed associations." All 14 AML deaths occurred 20 or more years after first exposure to formaldehyde. The NIOSH study is a large cohort with adequate follow up but limited industrial hygiene measurements of historical formaldehyde concentrations, as most workers were first exposed prior to 1970. Therefore, the study did not assign individual estimates of cumulative or peak exposure, and analyses for mortality due to various LHM including AML were performed using duration of exposure as a proxy for cumulative exposure. Information on smoking was also lacking.

3.1.1.2. Registry-based case control study of AML in Nordic countries. Talibov et al. (2014) analyzed 15,332 incident cases of AML diagnosed in Finland, Norway, Sweden, and Iceland from 1961 to 2005. The investigators matched 76,660 controls to cases by year of birth, sex, and country. Job titles and dates of assignment were linked to a job-exposure matrix (JEM) to estimate quantitative exposure to 26 workplace agents, including formaldehyde. No association was seen between risk of AML and increasing cumulative exposure to formaldehyde, after adjusting for exposure to solvents (aliphatic and alicyclic hydrocarbon solvents, benzene, toluene, trichloroethylene, methylene chloride, perchloroethylene, other organic solvents) and radiation (hazard ratio (HR) 0.89, 95% CI 0.81–0.97 for workers exposed to ≤ 0.171 ppm-years; HR 0.92, 95% CI 0.83–1.03 for workers exposed to 0.171–1.6 ppm-yrs, and HR 1.17, 95% CI 0.91–1.51 for > 1.6 ppm-years, compared to workers not exposed to formaldehyde). The strengths of this study were its exposure assessment based on a validatedJEM and the comprehensive ascertainment of incident AML cases (i.e., not deaths), resulting in high statistical power to detect increased risks, avoidance of survival bias, and the ability to consider and control for other possible leukemogens. One major limitation is the lack of data on smoking, which also is known to cause leukemia. This study failed to find an association between benzene and AML; however, increased risk of AML may be limited to those with exposure to very high concentrations that historically occurred only in a few occupational settings, e.g., the rubber hydrochloride industry (Infante et al., 1977; Schnatter et al., 2012).

3.1.1.3. European prospective investigation into cancer and nutrition (EPIC) cohort study. Saberi Hosnijeh et al. (2013) followed 241,465 subjects from 1992 through 2010 for a prospective study of lymphoid and myeloid leukemia risk in relation to occupation, nutrition and

metabolic risk factors. The European Prospective Investigation into Cancer (EPIC) investigators studied occupational risk factors among 477 incident leukemia cases (201 ML, including 113 AML, 237 lymphoid leukemia, and 39 other or unspecified leukemias) in France, Oxford (UK), the Netherlands, Sweden, Norway, and Italy (Saberi Hosnijeh et al., 2013). Occupational exposures were estimated using a general population JEM that classified occupational codes of study subjects by categories of high, low, and no exposure for 11 specific agents (e.g., benzene, trichloroethylene) or groups of agents (e.g., pesticides, chlorinated solvents). However, the authors reported that work histories were missing on a large number of cohort members, and these individuals had to be excluded. Study investigators lacked detailed job histories (job tasks and duration) for others, and the resulting exposure misclassification would be expected to be non-differential, attenuating risk estimates. On the other hand, this is one of the few studies examining specific subtypes of leukemia with risk estimates adjusted for smoking and other risk factors. AML risk was not increased among the formaldehyde low-exposure group (HR 1.01, 95% CI 0.65–1.57) after adjusting for sex, smoking status, alcohol intake, age at recruitment and country, and no AML cases occurred among individuals in the high-exposure category. An HR for chronic lymphocytic leukemia of 1.45 (95% CI 0.46–4.56) was reported among those with high exposure to formaldehyde, but this was based on 3 or fewer cases. ML risks were increased among those employed in chemical laboratories and shoe and leather workers, and weakly increased among those exposed to benzene but not those exposed to ionizing radiation (Saberi Hosnijeh et al., 2013).

3.1.1.4. UK formaldehyde users and producers cohort study. Coggon et al. (2014) updated mortality through 2012 for the UK cohort of 14,008 formaldehyde users and producers; however, the analysis grouped all ML and did not analyze AML mortality separately. Similar to other large industrial cohorts (Beane Freeman et al., 2009; Meyers et al., 2013), industrial hygiene measurements were not available in the early years and investigators estimated averages for job titles based on irritant symptoms and later measurements. Exposures were estimated to range from background (< 0.1 ppm), low exposure (0.1–0.5 ppm), moderate exposure (0.6–2.0 ppm) and high exposure (> 2 ppm). These exposure categories were similar to those estimated by Stewart et al. (1986) and applied in Beane Freeman et al. (2009). Moreover, a larger proportion (and greater number) of the UK cohort was exposed to high concentrations of formaldehyde (approximately 18% of the cohort) than the US cohort (approximately 4% of the cohort). Coggon et al., 2014 reported no increased mortality from ML (SMR 1.16, 95% CI 0.60–2.20 for background exposure; SMR 1.46, 95% CI 0.84–2.36 for low/moderate exposure; and SMR 0.93, 95% CI 0.450–1.82 for high exposure). In a nested case-control analysis of 45 ML (diagnosis from underlying or contributing cause of death or as a cancer registration) and 450 controls matched on factory and age, no significantly increased risk of leukemia was seen. Although ML risk was non-statistically significantly increased among workers exposed to high concentrations for < 1 year (OR 1.77, 95% CI 0.45–7.03), workers exposed to high concentrations ≥ 1 year showed no increased risk (OR 0.96, 95% CI 0.24–3.82) (Coggon et al., 2014).

3.1.1.5. Extended analysis of the NCI cohort study to evaluate specific types of myeloid leukemia. Checkoway et al. (2015) obtained the data from the NCI formaldehyde industrial workers cohort to further investigate specific types of leukemias, including AML (which had never been reported for this cohort), as well as performing an alternative analysis of peak exposure. The investigators reported that AML mortality was unrelated to cumulative exposure or peak exposure. Twelve of 34 AML deaths and 6 of 13 CML deaths occurred among study subjects with less than one year of employment. For workers employed at least one year, the risk of AML was highest (but not statistically significant) among workers with peak exposures of ≥ 2.0 to < 4 ppm (HR 1.78, 95% CI 0.61–5.25) and no trend was seen with increasing category of peak exposure (p for trend 0.37). In contrast, CML risks were greater, although the estimates were imprecise (HR 4.83, 95% CI 0.64–36.42 for peak exposure ≥ 2.0 to < 4 ppm based on 2 CML deaths and HR 5.32, 95% CI 0.81–34.90 for peak exposure ≥ 4 ppm based on 2 CML deaths).

3.1.2. Synthesis of epidemiology studies: exposure assessment issues identified by NRC

One of the major issues highlighted by the NRC peer review is that one exposure metric (peak exposure) was used to determine causality in the draft IRIS assessment, while a different exposure metric (cumulative exposure) was used for the dose-response evaluation to calculate an inhalation unit risk.

The NRC (2011) review of the Draft IRIS Assessment stated "the reliance on the peak exposure metric to determine causality rather than the more conventional dose metric of cumulative exposure should be further justified particularly in the absence of established modes of action" [p.112]. NRC further elaborated:

> "In the absence of evidence regarding exposure-disease mechanisms, as in the case of formaldehyde and LHP cancers, cumulative exposure is typically the default dose metric applied in epidemiologic analyses and risk assessment. But the most significant results were found for peak exposures, which have the greatest associated uncertainty. In view of the importance of this study, EPA should clarify the basis of its interpretations of the results regarding the various dose metrics and the various LHP cancers. Despite those concerns, the committee agrees that the NCI study is the most appropriate available to carry forward for calculation of the unit risk." (NRC, 2011, pp. 112–113)

The NRC recommended that the quality of exposure assessment relied upon in epidemiological evaluations should be explicitly evaluated when weighting and synthesizing epidemiological evidence. Where known causal relationships have been observed, exposure-response relationships often are seen with various exposure metrics, with stronger associations seen when more relevant metrics and exposure time windows are examined. Results such as those reported by Beane Freeman et al. (2009) are a good example of conflicting findings: the conventional exposure metric, cumulative exposure, demonstrated no association with risk of ML, whereas a surrogate of 'peak' exposure suggested one (Beane Freeman et al., 2009). When evaluating differences between cumulative exposure and peak exposure, and comparing risks associated with these, several differences should be highlighted.

NCI investigators (Beane Freeman et al., 2009; Blair et al., 1986; Hauptmann et al., 2003) defined peak exposure as the maximum peak, and the NCI investigators substituted the time-weighted average (TWA) for jobs without assigned peak exposures (Stewart et al., 1986). The authors reported a significant test for trend between peak formaldehyde exposure and leukemia, but only when unexposed subjects were included. Increased risk was not seen for higher peak exposure categories (2.0 to < 4.0 ppm, or ≥ 4.0 ppm) when compared to the lower peak category (> 0 to < 2.0 ppm). No association was reported with frequency of peak exposure, average intensity of exposure or with cumulative exposure to formaldehyde ("There was little evidence among formaldehyde workers of association for any lymphohematopoietic malignancy (LHM) with average intensity or cumulative exposure at the end of follow-up in 2004." (Beane Freeman et al., 2009, p. 751). In fact, a 10% deficit of ML deaths (acute and chronic types combined) was reported when compared to US population mortality rates. In an internal analysis, Beane Freeman et al. (2009) reported that ML deaths were not associated with the number or frequency of peaks. If there were a true association between peak exposure and leukemia, one would expect to see an association with number of peaks and not only ever having a (perhaps single) peak exposure. Hauptmann et al. (2003) acknowledged that "no measurements of peak exposure were available

in this study. Peak exposures were therefore estimated by an industrial hygienist from knowledge of the job tasks and a comparison with the 8-hour time-weighted average" (Hauptmann et al., 2003, p. 1616; Stewart et al., 1986). Stewart et al. (1986) reported that the exposure reconstruction included rating confidence (i.e., confident, less confident, not confident) in the exposure estimate; however, the "confidence" category appeared to apply to the "rank" exposure and not the "peak exposure." For example, if an IH specified "not confident" for an average exposure estimate, it is not clear how or if this information applied to the estimate of peak exposure (categorized during data collection as 1 = none, 2 = 0.1–0.5, 3 = 0.51–2.0, 4 = 2.1–4.0, 5 = > 4.0, 9 = unknown) (Stewart et al., 1986).

In extended analyses of the NCI cohort study, Checkoway et al. (2015) refined the classification of peak exposure. Workers who did not work in jobs identified as likely having peak exposures were classified as not exposed to peaks, and became the referent group. A total of 3478 cohort members were classified as having worked in jobs with estimated peak exposure of 2- < 4 ppm, and 2907 worked in jobs with estimated peak exposure of ≥ 4 ppm. Analysis by ML subtype (i.e., AML and CML deaths, separately) found no association between peak exposure and AML mortality (HR 1.71, 95% CI 0.72–4.07 and HR 1.43, 95% CI 0.56–3.63, respectively) (Checkoway et al., 2015). However, 13 of the 34 AML deaths were classified as having worked in jobs likely having peak exposure > 2.0 ppm, only 4 of which worked in these jobs within the 20 years preceding their AML death (i.e., latest exposure), and only one occurred (similar to the number expected) within the typical AML latency window of 2–15 years. Upon fuller analyses of these data, Checkoway et al. (2015) subsequently found that only a third of all the AML deaths were among cohort members assigned to categories with any peak exposure (i.e., > 2.0 ppm), nearly all of whom had their last peak exposure more than 20 years earlier, well outside of the maximum latency window.

Coggon et al. (2014) also reported that limited IH data were available for the UK formaldehyde users and producers cohort, preventing the derivation of quantitative metrics. Nevertheless, the investigators expressed high confidence that the high exposure category corresponded to average concentrations of at least 2 ppm. Industrial hygiene data also were limited in the US NCI industrial workers study, although the investigators used them as part of a detailed exposure reconstruction using best practices for such a reconstruction at the time. Stewart et al. (1986) reported that historical exposure levels were estimated because most companies did not begin sampling until the mid-1970's: they also monitored "present day" (i.e., early 1980's) operations to help extrapolate historical exposures. The NCI investigators relied upon exposure rank (six levels of TWA): trace, < 0.1 ppm, 0.1–0.5 ppm, 0.51–2.0 ppm and > 2 ppm.

One criticism leveled at the UK worker cohort study (Acheson et al., 1984; Coggon et al., 2003, 2014; Gardner et al., 1993) was that the "authors reported a concern about the quality of data when they made exposure assignments" (NRC, 2014b). This criticism seems to stem from the appropriate identification and discussion of study limitations by earlier UK investigators: Gardner et al. (1993) reported "when jobs were being placed into qualitative categories of exposure in the British study, some disagreement occurred as to which of two adjacent grades was most appropriate-for example, high or moderate? To achieve consistency across all the factories, the higher of the two was always used. It is not clear how differences were resolved in the United States study." Thus, there are no essential differences in the approach used by the UK investigators and the US investigators: both studies reported that limited data were available on quantitative exposure measures using existing industrial hygiene data (from the 1980s); both exposure assessments allowed for the consideration of changes in processes and exposure controls during the period of the study; and both used ranked categories of exposure, developed before the estimation process, based somewhat on subjective sensory experiences encountered in the job (e.g., odor occasionally present), and both used eye irritation and odor throughout the day to identify the highest intensity of exposure jobs (Acheson et al., 1984; Stewart et al., 1986).

Ultimately, the Beane Freeman et al. (2009) study alone does not (and cannot) provide reliable support for a conclusion that peak formaldehyde exposure causes ML or AML, especially considering the absence of peak measurement data in the US study, the results of the reanalysis by Checkoway et al. (2015), and the updated results from the UK study (Coggon et al., 2014), which used a more conservative approach to exposure estimation.

3.1.3. Synthesis of epidemiology studies: evaluation of the most specific diagnosis

The NRC (2011) raised the issue that diverse types of leukemias and lymphomas should not be grouped "because it combines many diverse cancers that are not closely related in etiology and cells of origin. Although the draft IRIS assessment explores specific diagnoses—such as AML and CML, as well as Hodgkin lymphoma and multiple myeloma (see, for example, EPA 2010, Tables 4–92)—the determinations of causality are made for the heterogeneous groupings of "all LHP cancers," "all leukemias," and "ML". When results for heterogeneous groupings are presented, there is no evidence of increased risk of all LHP cancers (Meyers et al., 2013; Beane Freeman et al., 2009) or all leukemias combined (Coggon et al., 2014; Meyers et al., 2013; Beane Freeman et al., 2009) in industrial cohorts when compared to general mortality rates. In addition, there is no evidence of exposure-response associations between all LHPs combined (or all leukemias combined) and cumulative exposure or average exposure (Beane Freeman et al., 2009) or duration of exposure (Meyers et al., 2013; Coggon et al., 2014).

Interestingly, the Draft IRIS Assessment noted that "Acute leukemias (ALL and AML), believed to arise from transformation of stem cells in the bone marrow, are less plausible. In contrast chronic lymphatic leukemia, lymphomas, multiple myelomas (from plasma B cells), and unspecified cancers may involve an etiology in peripheral tissues to include cells, cell aggregates, germinal centers, and lymph nodes. An association of these cancers to an exogenous agent acting at the POE [portal of entry] is biologically plausible" (EPA, 2010; page 4–190).

While the etiologies of most LHM are poorly understood, the possible role of environmental agents is plausible for AML, which has been linked with benzene, tobacco smoking, ionizing radiation and various cancer treatment agents, such as cisplastin, all of which have been classified by IARC as known human carcinogens that cause AML. It should be stressed that evidence exists that these agents, or their carcinogenic components, are capable of reaching the bone marrow. However, only six epidemiological studies of workers substantially exposed to formaldehyde published to date have published AML-specific results (Blair et al., 2001; Checkoway et al., 2015; Hauptmann et al., 2009; Meyers et al., 2013; Saberi Hosnijeh et al. 2013; Talibov et al., 2014), four of which were not available at the time of the IARC review or the release of the Draft IRIS Assessment. Saberi Hosnijeh et al. (2013) reported no association between "low" formaldehyde exposure and incidence of myeloid leukemia (HR 1.02, 95% CI 0.72–1.42 based on 49 cases exposed to formaldehyde and 130 unexposed cases). No differences were seen between subtypes: AML (HR 1.01, 95% CI 0.65–1.57) or CML (HR 0.92, 95% CI 0.46–1.84). No myeloid cases (and therefore no AML cases or CML cases) occurred among those classified as having "high" formaldehyde exposure (Saberi Hosnijeh et al., 2013). Talibov et al. (2014) found no association between formaldehyde and incident AML, after adjusting for exposure to specific solvents and ionizing radiation (HR 1.17, 95% CI 0.91–1.51 for 136 workers and 628 controls exposed to > 1.6 ppm-yrs). Meyers et al. (2013) reported a SMR for AML of 1.22 (95% CI 0.67–2.05) based on 14 observed AML deaths. Checkoway et al. (2015) performed AML-specific analysis using the NCI cohort, which had provided results only for all ML combined (Beane Freeman et al., 2009). When compared to US referent rates, AML mortality risk was decreased among workers

exposed to formaldehyde (SMR 0.80, 95 %CI 0.46–1.14) and internal analysis of exposure reported no trend with increasing cumulative exposure or peak exposure categories (Checkoway et al., 2015). Thus, new analyses of the NCI formaldehyde workers cohort specifically for AML detract from the hypothesis that formaldehyde causes AML.

The associations reported by Beane Freeman et al. (2009) between formaldehyde exposure and Hodgkin lymphoma and CML have not been observed in other studies (Meyers et al., 2013; Saberi Hosnijeh et al., 2013) and are less plausible, given the lack of known associations with Hodgkin lymphoma or CML and other chemicals or agents, such as benzene (Checkoway et al., 2015). Saberi Hosnijeh et al. (2013) reported a RR of 0.92 (95% 0.46 to 1.84) based on 46 CML cases. Meyers et al. (2013) reported a SMR of 1.35 (95% CI 0.44–3.15), based on 5 CML cases through 2008. The absence of established toxicological mechanisms for formaldehyde exposure and any of the LHM further weakens arguments for causation (Checkoway et al., 2012, 2015), especially given that inhaled formaldehyde appears incapable of reaching the bone marrow (discussed in Section 3.3).

3.2. Toxicological evidence

3.2.1. Animal evidence of formaldehyde-induced LHM

With regard to animal evidence of formaldehyde-induced LHM, the Draft IRIS Assessment (EPA, 2010) stated that the available animal evidence is limited, discussing mainly the results from the Battelle Columbus Laboratories (1981) study. The Draft IRIS assessment indicated that this study provides the only evidence of formaldehyde-induced LHM in animal models. However, the NRC (2011) peer review noted that although intriguing, EPA's unpublished re-analysis of the Battelle chronic experiments in mice and rats (Battelle Columbus Laboratories, 1981) contributed little to the weight of evidence evaluation.

In rats, Battelle Columbus Laboratories (1981) reported the incidence of leukemia (most of which were diagnosed as undifferentiated leukemia found sporadically in various organs) in male and female Fischer 344 rats following exposure to concentrations of 0, 2, 6, or 15 ppm for 24 months, followed by 6 months with no exposure. No concentration-related increases in the incidences of leukemia in either sex of rats were reported by Battelle Columbus Laboratories (1981), when a standard Fisher-Irwin exact test was applied (males $p = 0.0972$; females $p = 0.2316$).

Because of a significant number of early deaths in the high concentration group of both males and females, Battelle Columbus Laboratories (1981) also applied Tarone's extension to the Cox log-rank test (Tarone, 1975) to evaluate the leukemia incidence data. This test accounts for the number of animals at risk at each time point when the response of interest is observed. This adjustment assessed the probability of developing the endpoint of interest in those animals that did not survive until the termination of the study. The results of Tarone's extension indicated that the incidence among female rats in the high concentration group was statistically significant ($p = 0.0056$, not 0.0003 as reported[3]); however, no association was seen in the male rats exposed at high concentrations ($p = 0.6891$). No concentration-related increase in leukemia was observed in the female rats exposed at either 2 ppm or 6 ppm, and no survival problems were noted. Even after application of Tarone's extension, leukemia in male or female rats was not identified in the Battelle Columbus Laboratories (1981) study as an endpoint related to formaldehyde exposure, nor was it so designated in two publications citing this study (Kerns et al., 1983; Swenberg et al., 2013).

More contemporary statistical methods, such as the Cochran-Armitage and the Poly3 (Bailer and Portier, 1988; Peddada and Kissling, 2006) trend tests, have replaced those used in the early 1980's. The Poly3 trend test is a survival-adjusted quantal-response procedure that modifies the Cochran-Armitage linear trend test to take inter-group survival differences into account. Importantly, the Poly3 test is the test currently used by the National Toxicology Program (NTP) to evaluate incidence data both for trend and pair-wise comparisons, to assess the probability of the response in the presence of inter-current mortality. The results of the application of these tests indicated p values of 0.43 and 0.82 for the Poly3 and Cochran-Armitage, respectively, demonstrating no association.

In mice, the Draft IRIS Assessment (EPA, 2010) suggested that the "adjusted" incidence of lymphoma in female mice, when the 6-month sacrifice animals were removed from consideration (because tissues outside of the respiratory tract were not examined), was statistically significant ($p < 0.05$) in animals exposed to 15 ppm formaldehyde, compared to untreated controls. However, as indicated in the methods for the Battelle Columbus Laboratories (1981) study, statistical significance, when applying the Tarone extension of the Cox test, is achieved with a p value of 0.05 divided by the number of dose groups. In the case of the Battelle Columbus Laboratories (1981) study for the mouse data, statistical significance would be $p < 0.0167$, as noted in the summary tables (Table 8 of the Battelle Columbus Laboratories (1981) report); therefore, based on this criterion, this endpoint was not considered statistically significant. As with the leukemia incidence in rats, the Battelle study authors did not report lymphoma in mice as an endpoint related to formaldehyde exposure.

Since 2010, two short-term carcinogenicity studies have been conducted and published (as a Technical Report) by the NTP of NIEHS in strains of genetically predisposed mice (male C3B6·129F1-Trp53tm1Brdp53 haplo-insufficient mice and male B6.129-Trp53tm1Brd) (Morgan et al., 2017). These short-term carcinogenicity studies were conducted to test the hypothesis that formaldehyde inhalation would result in an increased incidence and/or shortened latency to nasal and lymphohematopoietic tumors and to investigate hypotheses that formaldehyde may induce leukemia by a mechanism not involving DNA adduct formation. This proposed mechanism assumes that inhaled FA could cause significant genetic damage to stem cells in the nasal epithelium or circulating in local blood vessels. These damaged stem cells could reach the general circulation, home to tissues that support the hematopoietic niche, undergo lodgement and become leukemic stem cells. The animals were exposed to 7.5 or 15 ppm formaldehyde 6 hours/day, 5 days/week, for 8 weeks. The investigators reported that because the doubling time for hematopoietic stem and progenitor cells (HSPCs) is between 2 and 4 weeks, and the entire HSPC pool turns over every 8 weeks, an 8 week exposure duration was considered sufficient to investigate the hypothesized mechanism for inducing leukemia. Following the 8-week inhalation exposure, mice were monitored for approximately 32 weeks (until approximately 50 weeks of age). At the highest concentrations, significant cell proliferation and squamous metaplasia of the nasal epithelium were observed; however, no nasal tumors were observed. No cases of leukemia were seen in either strain and a low incidence of lymphoma in exposed mice was not considered related to exposure. In addition, no significant changes in haematological parameters were noted. Under the conditions of these studies, the authors concluded that formaldehyde inhalation did not cause leukemia in these strains of genetically predisposed mice (Morgan et al., 2017).

Overall, the weight of evidence from animal studies reported in the Draft IRIS Assessment (EPA, 2010) did not support an association between formaldehyde exposure and LHM. Since that time, additional studies (Morgan et al., 2017) have provided evidence that suggests a lack of association between formaldehyde exposure and LHM. In addition, no evidence of changes in blood parameters that might be

[3] This appears to be a misreading of the Battelle report. In the Battelle Report Volume A Table 10 – Analysis of Effects of Formaldehyde in Female Rats - reports a p-value of 0.0056 from the Adjusted Cox/Tarone pair-wise comparison of the control to 15 ppm for Leukemia, all. The next row in that table with an endpoint of Uterus, Endometrial Stromal Polyp is the one that reports a p-value of 0.0003 for the pair-wise analysis of control to 15 ppm.

associated with leukemias has been reported in any animal studies exposed to formaldehyde at high concentrations following both acute and chronic durations (Appelman et al., 1988; Dean et al., 1984; Johannsen et al., 1986; Kamata et al., 1997; Kerns et al., 1983; Til et al., 1988, 1989; Tobe et al., 1989; Vargova et al. 1993; Woutersen et al., 1987). Among these studies, Vargová et al. (1993) reported increased red blood cell counts and increased proportions of lymphocytes and monocytes in rats, rather than decreases, following exposure to formaldehyde by gavage at 80 mg/kg/day for 28 days.

3.3. Mode of Action Evidence

3.3.1. Improve understanding of when exogenous formaldehyde exposure appreciably alters normal endogenous formaldehyde concentrations

NRC (2011) recommended that one key improvement to the science would be an understanding of when exogenous formaldehyde exposure altered normal endogenous formaldehyde concentrations. Because formaldehyde is endogenously present, it is important to differentiate levels that are due to normal metabolic processes from levels that might be present as a result of exogenous exposure. A number of studies have applied sensitive methods to differentiate exogenous and endogenous levels of formaldehyde in tissues (Casanova-Schmitz et al., 1984; Lu et al., 2010, 2011; Moeller et al., 2011; Swenberg et al., 2011).

The results of these studies with highly sensitive instruments and accurate assays indicate that inhaled formaldehyde was present in the nasal respiratory epithelium, but not other tissues beyond the site of initial contact. In contrast, endogenous adducts were readily detected in all tissues examined. Moreover, the amounts of exogenous formaldehyde-induced adducts were 3- to 8-fold and 5- to 11-fold lower than the average amounts of endogenous formaldehyde-induced adducts in rat and monkey nasal respiratory epithelium, respectively (Yu et al., 2015).

An additional study conducted in rats exposed to ^{13}C-formaldehyde (Kleinnijenhuis et al., 2013) provided results consistent with those from studies focused on measuring endogenous versus exogenous DNA adducts. In this study, Sprague-Dawley rats were exposed nose-only to 10 ppm ^{13}C-formaldehyde for 6 hours and blood concentrations evaluated during exposure and for 30 minutes following exposure. This study was conducted specifically to investigate the mechanism proposed by Zhang et al. (2010a) that formaldehyde is absorbed during respiration and could reach any target tissue, such as the bone marrow, via the blood in the form of methanediol to exert its genotoxic activity. Exogenous ^{13}C-formaldehyde was not detectable in the blood of rats either during or up to 30 min after the exposure. The authors concluded that "it is highly unlikely that the mechanism proposed by Zhang et al. (2009), that exposure to FA by inhalation may lead to an increased FA concentration in blood and as such may cause leukemia, is true" (Kleinnijenhuis et al., 2013).

New studies have been conducted to investigate the potential toxicity/carcinogenicity of endogenous formaldehyde. The most recent studies demonstrate that endogenous formaldehyde in bone marrow is toxic, and probably carcinogenic, and therefore may increase leukemia risk (Pontel et al., 2015; Lai et al., 2016).

3.3.2. Reconcile divergent statements regarding systemic delivery

Multiple studies in rats (Lu et al., 2011; Yu et al., 2015; Edrissi et al., 2013) and monkeys (Moeller et al., 2011; Yu et al., 2015) conducted with sensitive analytical methods that can measure endogenous versus exogenous formaldehyde DNA or protein adducts have demonstrated that inhaled exogenous formaldehyde is not systemically absorbed or reaches sites distant from the point of initial contact. In addition to these studies, the available data on the toxicokinetics of formaldehyde suggest that no significant amount of "free" formaldehyde would be transported beyond the portal of entry.

In addition to studies supporting the lack of systemic delivery of formaldehyde, anatomically accurate computational fluid dynamics (CFD) models of the rat, monkey, and human have been applied to evaluate the effects of endogenously present formaldehyde on uptake from the respiratory tract. The consideration of endogenous formaldehyde concentrations in nasal tissues did not affect flux or nasal uptake predictions at exposure concentrations > 500 parts per billion (ppb); however, reduced nasal uptake was predicted at lower exposure concentrations (Schroeter et al., 2014).

3.3.3. Data are insufficient to conclude formaldehyde is causing cytogenetic effects at distant sites

The modes of action that have been proposed in the Draft IRIS Assessment (EPA, 2010) to cause leukemogenesis rely strongly on the hypothesis that exposure to inhaled formaldehyde can result in cytogenetic effects at sites distant from the portal of entry. While the NRC (2011) noted that numerous studies have shown genotoxic effects in cells exposed in vitro, and a few studies have shown positive cytogenetic effects in circulating blood lymphocytes in heavily-exposed workers, they also noted that it is unlikely that these effects are relevant to a possible leukemogenic effect of formaldehyde, particularly at low exposure levels. The potential leukemogenic effect and exposure-response relationships at lower exposure levels have been comprehensively evaluated by Nielsen et al. (2013, 2017).

One key study cited in multiple agency evaluations as providing evidence of cytogenetic events in the development of leukemias is by Zhang et al. (2010a, 2010b) compared the prevalence of markers of hematopoietic function and chromosomal aneuploidy among workers occupationally exposed to formaldehyde with those of a group of unexposed workers in China. Ninety-four workers were included, with 43 workers occupationally exposed to formaldehyde and 51 workers unexposed to formaldehyde as controls. The authors reported a higher prevalence of monosomy 7 (loss of a chromosome) and trisomy 8 (gain of a chromosome) in metaphase spreads prepared from cultures of CFU-GM colony cells. The authors suggested that this demonstrated that formaldehyde exposure was associated with an increase in leukemia-specific chromosomal aneuploidy in vivo in the hematopoietic progenitor cells of the exposed workers. However, no direct in vivo metaphases had been examined in workers blood. Furthermore, this was a cross-sectional comparison of blood and cytogenetic measures between two groups, and observed differences could not be established as resulting from formaldehyde exposure or due to other overall differences between the two groups.

Two re-analyses of the underlying data from the Zhang et al. (2010a) study have been published (Gentry et al., 2013; Mundt et al., 2017). The first (Gentry et al., 2013) relied upon selected underlying data provided through a Freedom of Information Act request that included: 1) individual data on blood cell counts in both formaldehyde-exposed and unexposed individuals including any data on health status of these individuals; 2) individual data on the FISH results for monosomy 7 and trisomy 8 for cultures of samples obtained from 10 formaldehyde-exposed workers and 12 unexposed controls; 3) data on additional chromosomal abnormalities examined and/or observed; and 4) details of the methods sufficient for a qualified scientist to replicate the results reported in the Zhang et al. (2010) study. The results of this reanalysis suggested that factors other than formaldehyde exposure likely contributed to the reported findings. In addition, although the authors stated in their paper that "all scorable metaphase spreads on each slide were analyzed, and a minimum of 150 cells per subject was scored," this protocol was not followed specifically for chromosome 7 or chromosome 8 (recent correspondence indicates a minimum of 150 total metaphases were scored for 24 chromosomes per subject). Far too few cells were counted to draw any meaningful conclusions, and far fewer than the approximately 400 per chromosome cited in previous analyses in which the protocol was described (Zhang et al., 2005, 2011). In addition, the assays used (CFU-GM) do not actually measure the proposed events in primitive cells involved in the development of AML. Evaluation of these data indicates that the aneuploidy measured

could not have arisen in vivo, but rather arose during in vitro culture.

In 2014, Mundt et al. requested the individual exposure measurement data for each of the participants in the Zhang et al. (2010a) study from NCI. In 2016, the request was in part granted and the mean formaldehyde estimate for each exposed worker (but not the individual exposure measurement values) was provided via a Technology Transfer Agreement (TTA) with NCI. Using these data, the Gentry et al. (2013) reanalysis was extended to include exposure-response analyses. Results of this second reanalysis showed that differences seen at the group comparison level, i.e., comparing the prevalence of white blood cell, granulocyte, platelet, and red blood cell counts at the group level in fact were independent of measured formaldehyde exposure level. Among exposed workers, no association was observed between individual average formaldehyde exposure estimates and frequency of aneuploidy, suggested by the original study authors to be indicators of ML risk. Differences between the two groups of workers, other than formaldehyde exposure, were therefore likely to explain the results reported by Zhang et al. (2010a).

Subsequent studies of the same population of formaldehyde-exposed and non-exposed workers in China (Lan et al., 2015; Seow et al., 2015; Bassig et al., 2016) have been suggested by the authors to confirm the results of Zhang et al. (2010a); however, many of these studies report results from the same biological samples as Zhang et al. (2010a) and therefore, do not provide replication of the results. The repeated use of the original Zhang et al. (2010a) data, and its implications, have been reiterated (Pira et al., 2017; Gentry et al., 2013; Speit et al., 2010) and the original authors have responded to some of the criticisms (Rothman et al., 2017; Lan et al., 2015; Zhang et al., 2010b). Replication of the Zhang et al. (2010a) results will require replication in an independent population of formaldehyde-exposed workers, and where methodological issues are adequately addressed. An attempt to replicate the results could be conducted in the same population of workers as Zhang et al. (2010a) and Lan et al. (2015) in which the median exposures to 43 workers were 1.28 ppm (10th and 90th percentile: 0.63, 2.51 ppm). However, as noted previously (Section 3.1.1), no evidence of an association between formaldehyde exposure and leukemias has been reported in multiple recent epidemiological studies with large numbers of subjects that have been exposed to concentrations > 2.0 ppm. The increasing evidence that inhaled formaldehyde does not move beyond the portal of entry (Section 3.3.2) also calls into question many of the conclusions from Zhang et al. (2010a).

Albertini and Kaden (2016) reviewed the body of data that reportedly indicates genetic changes in circulating blood cells and in blood-borne hematopoietic precursor cells (HPCs). These changes have been considered to be indicators that systemic genotoxicity occurs after human inhalation exposure to formaldehyde, although the mechanisms by which this could occur remain unknown. For each study, the authors examined the sources of exposure, possible co-exposures, biomarkers for internal exposures and genetic signatures of formaldehyde effects.

In reviewing the available studies, many genetic changes in blood cells were noted by Albertini and Kaden (2016), with a contrast in results between animal and human studies: the majority of animal studies were negative and the majority of human studies were positive. This pattern was attributed to the difference in target cell being studied, with bone marrow cells studied in animals and peripheral blood lymphocytes studied in humans. Exposure of human cells to formaldehyde at sites of contact in vivo could provide opportunities for exposure of T-lymphocytes to formaldehyde or products of oxidative stress, which could result in the genetic changes observed in peripheral blood cells. However, these results are inconsistent with results from controlled animal studies, discussed previously, that demonstrate - by labeling administered formaldehyde - inhaled (exogenous) formaldehyde does not travel beyond the portal of entry (Casanova-Schmitz et al., 1984; Lu et al., 2010, 2011; Moeller et al., 2011; Swenberg et al., 2011). Therefore, these types of genetic changes reported in human studies do not provide evidence that formaldehyde moves beyond the portal of entry to the bone marrow, which would be necessary to result in direct induction of chromosome-level mutations in the bone marrow. Despite the apparent inability of exogenous formaldehyde to reach the bone marrow, the mutagenic effects of formaldehyde in bone marrow have not been tested in humans.

Albertini and Kaden (2016) concluded that overall, the available literature on genetic changes following formaldehyde exposure did not provide convincing evidence that exogenous exposure, and specifically exposure by inhalation, induces mutations as a direct DNA-reactive effect at sites distant from the portal-of-entry tissue. This would include proposed mode of actions that involve a stem cell effect at the portal of entry with circulation back to the bone marrow. Such exposures have not been shown to induce mutations in the bone marrow or in any other tissues beyond the point of contact. Thus, the weight of scientific evidence does not provide biological plausibility of lymphohematopoietic cancers, as proposed by EPA (2010) and NTP (2011).

3.4. Dose-response assessment

Several NRC (2011) peer-review comments were raised regarding the dose-response assessment conducted by EPA in the Draft IRIS Assessment (2010). One comment highlighted the need to conduct independent analyses of the dose-response models, using the data from the Beane Freeman et al. (2009) study to confirm which models fit the data appropriately (NRC, 2011). Using the original data from the key study (Beane Freeman et al., 2009) and documentation provided in the Draft IRIS Assessment, Van Landingham et al. (2016) attempted to duplicate the reported inhalation unit risk (IUR) values for Hodgkin lymphoma and all leukemias and address the NRC Committee's questions regarding application of the appropriate dose-response model. Overall, there was difficulty duplicating the IURs reported by EPA (2010), largely due to a lack of critical information provided in the IRIS documentation. Perhaps most problematic, the first step of the analysis did not determine significant exposure-response relationships between formaldehyde and lymphohematopoietic endpoints for the metric (cumulative exposure) needed in the estimation of an IUR. The authors concluded that the resulting analysis, while it could be mechanically performed, provided no valid or useful insights on the risks of formaldehyde exposure. The lack of apparent exposure-response relationships for selected endpoints raises the question whether quantitative analyses are appropriate for these endpoints, and if so, how results are to be interpreted.

The NRC (2011) also noted the need to consider alternative extrapolation models for analyzing the cancer data. In 2013, Starr and Swenberg proposed a novel "bottom-up" approach for bounding low-dose human cancer risks using formaldehyde as an example (Starr and Swenberg, 2013). This approach requires information on background risk, background or endogenous exposure and the additional exogenous exposure of interest. The results of this approach provided estimates of risk ($< 3.9 \times 10^{-6}$) that were more than 14,000-fold lower than the corresponding Draft IRIS Assessment (EPA, 2010) estimate for all leukemias (5.7×10^{-2}) and considers the impact of background endogenous formaldehyde concentrations, which is not considered in the Draft IRIS Assessment (EPA, 2010). In 2016, Starr and Swenberg provided an update to this approach, incorporating new formaldehyde-DNA adduct data, and allowing for uncertainty in two of the parameters (background cancer risk and background endogenous concentrations of formaldehyde) (Starr and Swenberg, 2016). Consideration of the statistical uncertainty in these two parameters resulted in estimates of risk for leukemias that were even smaller than those initially estimated in Starr and Swenberg (2013). The authors concluded that these estimates provide a reality check for the IUR presented in the Draft IRIS Assessment (EPA, 2010). In addition, the large discrepancy between results using an approach that relies on molecular dosimetry data (i.e., the bottom up approach) versus one that relies upon uncertain retrospective occupational exposure reconstructions (i.e., the approach

relied upon in EPA (2010) call into question the credibility of attributing increases in human mortality from leukemias to occupational exposure to formaldehyde.

3.5. Methods for evidence integration

The NRC (2011) noted that the Draft IRIS Assessment's (EPA, 2010) approach to weight of evidence should include "a single integrative step after assessing all of the individual lines of evidence". Although a synthesis and summary are provided, the process that EPA used to weigh different lines of evidence and how that evidence was integrated into a final conclusion are not apparent in the draft assessment and should be made clear in the final version.

Since the Draft IRIS Assessment (EPA, 2010) and the NRC (2011) peer review, several frameworks have been developed to integrate evidence across different lines of scientific inquiry including epidemiology, toxicology and mode of action studies (Adami et al., 2011; Lavelle et al., 2012; Linkov et al., 2015; Rhomberg, 2015b; Rooney et al., 2014; Woodruff and Sutton, 2014). The EPA has also proposed preliminary approaches for integrating evidence in response to the NRC (2011) peer review of formaldehyde (EPA, 2013a).

Rhomberg et al. (2011) applied a hypothesis-based weight of evidence approach to evaluate formaldehyde and leukemogenesis, considering how human, animal and mode of action results inform one another. In comparing the potential alternative proposals for causality, the authors concluded that the evidence for a causal association between formaldehyde exposure and leukemia is not only weak but strains biological plausibility (Rhomberg et al., 2011).

Nielsen et al. (2017) also considered the body of formaldehyde research while re-evaluating the WHO (2010) formaldehyde indoor air quality guideline for cancer risk assessment. Nielsen et al. (2017) iterated that although formaldehyde is genotoxic and causes DNA adduct formation, it is also clastogenic. Exposure-response relationships from both animal and human data were nonlinear, and relevant genetic polymorphisms had not been identified. Although one epidemiological study had reported an association with nasopharyngeal cancer and others reported inconsistent associations with leukemias, relative risks were not increased below 1 ppm (mean exposures). Because inhaled formaldehyde does not pass beyond the respiratory epithelium, any direct effects are limited to portal-of-entry effects (Nielsen et al., 2017).

Other reviews and syntheses of evidence focused on epidemiological studies, and this body of literature has been most variably interpreted. In 2014, an independent National Research Council committee was charged with performing a peer review of the NTP evaluation of formaldehyde for the 12th edition of the RoC (NRC, 2014b). This NRC committee produced a new definition for "sufficient evidence" of carcinogenicity as demonstrated by two or more strong or moderately strong epidemiological studies with different study designs and populations showing associations between formaldehyde exposure and a specific cancer type. In this approach, "strong" epidemiology studies do not refer to the magnitude of the association, but relect a judgment of study quality and utility made by reviewers who considered chance, bias, and confounding as alternative explanations for the observed association and found these were not reasonable explanations. Further, "strong" epidemiology studies comprised large populations with long durations of exposure and an adequate follow up period to allow for latency, and had exposure assessments that were able to discriminate between "high" and "low" formaldehyde exposure categories. This "strength of evidence" approach contrasts with a "weight of evidence approach." Although each epidemiology study was classified as one of three categories (strong, moderately strong, or weak), this approach suggests that 2 or more strong or moderately strong studies with positive results are enough to conclude sufficient evidence of carcinogenicity exists, and discounts epidemiology and animal studies that are negative or contradictory.

Meta-analyses are often used to synthesize findings across many epidemiology studies, identifying sources of potential heterogeneity which then can be explored in interpreting the overall evidence. In the Draft IRIS Assessment (EPA, 2010), meta-analyses conducted by several investigators were considered (Zhang et al., 2009; Collins and Lineker, 2004; Bosetti et al., 2008). Since then, two additional meta-analyses were conducted (Bachand et al., 2010; Schwilk et al., 2010). Bachand et al. (2010) excluded lower-quality studies and reported a meta-RR of 1.05 (95% CI 0.93–1.20) based on 16 cohort studies and a meta-OR of 0.99 (95% CI 0.71–1.37) based on 2 case-control studies for all leukemia, reported separately due to heterogeneity. Schwilk et al. (2010) published a meta-analysis of the epidemiological findings on myeloid leukemia, but limited to the highest-exposed sub-group reported in four studies (three cohort and one case-control): RR = 2.47; 95% CI, 1.42 to 4.27. Checkoway et al. (2012) conducted a critical review and synthesis of the epidemiological evidence and concluded that results from epidemiological studies were not consistent and did not show strong results or exposure-response associations. None of these reviews, however, included the results from the extended follow up of the NIOSH garment workers study (Meyers et al., 2013), the extended follow up of the UK producers and users (Coggon et al., 2014) or the extended analyses of the NCI cohort (Checkoway et al., 2015). In addition, meta-analyses and/or critical reviews of epidemiological literature require further integration with other lines of evidence.

4. Conclusions

It has been seven years since the release of the Draft IRIS Toxicological Review of Formaldehyde (EPA, 2010). In peer-reviewing this draft report, an NRC Committee raised many substantive questions related specifically to the conclusions drawn in the document and the quantitative estimates of potential toxicity (NRC, 2011). This Committee was tasked with reviewing and commenting on information provided in the draft assessment, and did not independently conduct a review of the primary literature, but did determine that many of EPA's conclusions were not supported by the information and studies cited in the draft assessment. The committee also identified general methodologic problems with the Draft IRIS Assessment, and provided specific comments related to the evaluation of specific studies and conclusions based on the available evidence. The comments related to a causal association between formaldehyde exposure and LHM largely involved the interpretation of the available evidence at that time and the framework in which it was evaluated by EPA (2010). The committee found that EPA's preliminary conclusion that formaldehyde causes leukemia, ML or related hematopoietic cancers appeared to be "subjective' in nature, and that no clear scientific framework had been applied by EPA in reaching that conclusion. The absence of such a framework was judged by the committee as troublesome, given that the scientific evidence on the question was weak (NRC, 2011).

Since the NRC (2011) peer review, significant additional scientific evidence has become available that addresses many of the questions raised by the NRC Committee regarding a causal association between formaldehyde exposure and LHM. Some of these new studies and analyses were conducted in response to the NRC (2011) comments and recommendations, while others reflect ongoing work and updates of studies on this topic. All add to the scientific evidence surrounding the potential causal relationship between formaldehyde inhalation exposure and LHM, and should be addressed in the critical evaluations and integration of evidence presented in an updated IRIS Assessment.

Also since the NRC (2011) peer review, the EPA has proposed enhancements to the IRIS process (EPA, 2013b) that incorporate many of the general recommendations made by the NRC (2011) related to methodological issues. This process involves the evaluation and synthesis of evidence within separate streams of evidence (human, animal and mechanistic). However, in a critical review of the process conducted by a separate NRC Committee, while there was improvement in guidelines for evaluation and synthesis of evidence within an

evidence stream, the NRC Committee still noted limitations in synthesizing or integrating evidence across streams or categories (NRC, 2014a).

Nearly all of the recently available evidence from multiple lines of evidence, especially those studies that have been focused on addressing comments from the NRC Committee reviewing the Draft IRIS Assessment (NRC, 2011), have increased the weight of evidence favoring a conclusion of a lack of a causal association between formaldehyde exposure and LHM. The Checkoway et al. (2015) re-analysis using the data from the Beane Freeman et al. (2009) study was able to address directly several questions and comments from the NRC (2011) Committee, as the Draft IRIS Assessment (2010) was highly dependent on this study for drawing both qualitative and quantitative conclusions related to formaldehyde leukemogenicity and risk of LHM following inhalation exposure to formaldehyde. The Checkoway et al. (2015) reanalysis provides several results and insights relevant for assessing the risk of specific LHM. Not the least of these, the AML-specific results provide no support for the conclusion that formaldehyde causes AML. Associations seen between formaldehyde exposure and Hodgkin lymphoma and CML are inconsistent with other studies and also lack a plausible biological mechanism (Checkoway et al., 2015). NTP (2011) also noted that because the evidence for Hodgkin lymphoma is mainly limited to the NCI cohort study, a causal association cannot be established. No other LHM was associated with either cumulative or peak formaldehyde exposure. These results of the fuller analysis of the data from Beane Freeman et al. (2009) are consistent with recent epidemiological studies (Meyers et al., 2013; Saberi Hosnijeh et al. 2013; Talibov et al., 2014) which report no significant increase in LHM, specifically AML, among cohorts of workers exposed to formaldehyde.

The available animal evidence did not support a causal association between formaldehyde exposure and LHM at the time the Draft IRIS Assessment (EPA, 2010) was released. Since that time, additional studies have been conducted by the NTP using two sensitive assays in mice genetically predisposed to develop cancer following short-term exposure to a chemical (Morgan et al., 2017). These studies provided no evidence of changes in endpoints related to LHM or the presence of any LHM following exposure to high concentrations (15 ppm) of formaldehyde.

Studies conducted to evaluate potential mechanisms associated with formaldehyde exposure and LHM have demonstrated a lack of evidence for exogenous formaldehyde to move beyond the portal of entry. Multiple studies conducted in multiple species using highly sensitive techniques (Edrissi et al., 2013; Lu et al., 2011; Moeller et al., 2011; Yu et al., 2015) have demonstrated that while endogenous formaldehyde is present in all tissues, exogenous formaldehyde following inhalation exposure is not transported systemically. While some mechanisms for the development of LHM following inhalation exposure to formaldehyde have been hypothesized (EPA, 2010; Zhang et al., 2009, 2010a), there is no evidence to support these proposed mechanisms and the NRC Committee noted that:

> "Although EPA postulated that formaldehyde could reach the bone marrow either as methanediol or as a byproduct of nonenzymatic reactions with glutathione, numerous studies described above have demonstrated that systemic delivery of formaldehyde is highly unlikely at concentrations below those which overwhelm metabolism according to sensitive and selective analytic methods that can differentiate endogenous from exogenous exposures." (NRC, 2011; page 45)

The more recent research all but confirms this. Several modes of action have been proposed, relying primarily on data reported by Zhang et al. (2010a) as well as subsequent evaluations of the same population of Chinese workers (Bassig et al., 2016; Lan et al., 2015; Seow et al., 2015). These include a mode of action in which risk of ML is increased due to immune suppression resulting from formaldehyde exposure (Bassig et al., 2016; Seow et al., 2015). The speculated modes of action, however, assume systemic delivery of formaldehyde except one, which is a hypothesized mode of action in which hematopoietic cells in the nasal epithelium that are impacted by exposure to formaldehyde return to the bone marrow. The NRC Committee considered this proposed mode of action and concluded that:

> "As a result, EPA could only speculate that circulating hematopoietic stem cells that percolate through nasal capillary beds or nasal-associated lymphoid tissues may be the target cells for mutations and clastogenic effects that eventually result in lymphohemotopoietic cancers. Experimental evidence of [this] mechanism is lacking." (NRC, 2011; page 45)

This currently leaves no acceptable proposed mode of action for the development of LHM following inhalation exposure to formaldehyde that can be scientifically substantiated.

The available toxicokinetic data also do not support the transport of inhaled formaldehyde from the portal of entry. The studies by Swenberg and colleagues unequivocally demonstrate that exogenous formaldehyde exposure does not increase formaldehyde concentrations measured in any internal tissues over those in unexposed animals, i.e., endogenously produced formaldehyde is the predominant if not only source of internal formaldehyde (Edrissi et al., 2013; Lu et al., 2010, 2011; Moeller et al., 2011; Swenberg et al., 2011; Yu et al., 2015).

The biological plausibility of a mode of action for the development of LHM following inhalation exposure to formaldehyde has relied heavily upon the incompletely reported results from the Zhang et al. (2010a) study in which the authors report differences between groups of formaldehyde exposed and unexposed groups in the frequency of monosomy 7 (loss of chromosome) and trisomy 8 (gain of chromosome), based on metaphase spreads prepared from culture of CFU-GM colony cells. However, reanalysis of the underlying raw data in two studies (Gentry et al., 2013; Mundt et al., 2017) have identified methodological problems with this study that challenge these conclusions, as well as demonstrate a lack of association between level of formaldehyde exposure and the observed aneuploidy (or any of the haematological measures).

Overall, the quality and amount of evidence relevant to the understanding of a potential causal relationship between formaldehyde inhalation exposure and risk of LHM has increased substantially since the completion of the Draft IRIS Assessment (EPA, 2010) and release of the NRC peer review (NRC, 2011). New evidence has been published in each of the major streams of evidence (i.e., human, animal and mechanistic) that consistently indicates a lack of a causal association between formaldehyde exposure and LHM, and specifically AML. These new studies have addressed many of the NRC (2011) scientific criticisms surrounding the evaluation of a combination of cancer types, as well as increased our understanding of the potential impact of exogenous exposure on endogenous levels, which is critical in attempting to understand the potential hazards or risks from formaldehyde exposure. Regardless of which of the several similar approaches to integrating the available evidence between formaldehyde inhalation exposure and the potential for leukemia risk, there is at most only limited suggestive positive evidence, in contrast with the bulk of evidence suggesting no such association. Therefore, a conclusion of causation is not justified scientifically. The scientific landscape into which EPA will release its long-anticipated revised IRIS Toxicological Review of Formaldehyde – Inhalation Assessment is very different from that of the 2010 Draft IRIS Assessment, both in terms of improved methodological approaches and the available epidemiological, toxicological and mechanistic evidence. Given formaldehyde's commercial importance, ubiquity in the environment and endogenous production, accurate determination of whether occupational, residential, or consumer exposure to formaldehyde causes leukemia or any type of human neoplasm is critical.

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